REMARKS

Status of claims

Claims 1, 3-6, 8, 10-13, 33, 34 and 37-42 are pending.

Claims 1, 3-6, 8, 10-13, 33, 34 and 37-42 have been rejected.

By way of this amendment claims 1, 3, 4, 6, 12, 13, and 42 are amended.

Upon entry of this amendment, claims 1, 3-6, 8, 10, 12, 13, 33, 34 and 37-42 will be pending.

Summary of the Amendment

Claims 1, 3, 4, 6, 12, 13, and 42 have been amended to incorporate specific references to the types of non-cellular particles and/or nucleic acid molecules used in various embodiments defined by the claimed methods. Support for the amendment is found throughout the specification and originally filed claims. No new matter is added.

Claim Objections

Claim 42 stands objected to under 37 C.F.R. § 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. The Office alleges that the scope of claim 42 is broader than the base claim because it allegedly includes a viral particle, while the base claims exclude a viral particle. Applicants have amended claim 42 to remove the recitation of "a viral particle" rendering the objection moot.

In view of the foregoing, Applicants respectfully request that the objection be withdrawn.

Claim Rejections under 35 USC § 112, second paragraph

Claims 1, 3-6, 8, 10, 12, 13, 33, 34, and 37-42 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office alleges that the

> Claims are vague and indefinite because of claim recitation "a cationic amphiphile/DNA complex." It is noted the specification does not specifically define the ...[term]..., thus, given the plain meaning, it encompasses any deoxynucleic acid material including a DNA virus such as adenovirus.

(Office Action, page 3). Applicants respectfully disagree. The phrase "cationic amphiphile/DNA complex" is explicitly defined (see, for example, page 5, lines 18-19). Furthermore, Applicants have added the limitation that the compound is a "plasmid." Accordingly, the claims are not vague and indefinite because one of skill in the art would clearly understand the meaning of the term.

Claims 12 stands rejected under 35 U.S.C. § 112, second paragraph because it does not sufficient antecedent basis for the limitation "said non-cellular particle" in the claim. Claim 12 has been amended rendering the rejection moot.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claim Rejections under 35 USC § 112, first paragraph

Claims 1, 3-6, 8, 10-13, 32-34 and 37-42 stand rejected under 35 U.S.C. 112, first paragraph, for the reasons of record (Paper 14) that are also addressed in the current Official Action, i.e. as containing subject matter which is alleged to as not being described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully disagree.

The Office alleges that the compound of the pending claims does not exclude an adenoviral vector in the particle and thereof the contrary evidence present in *Guibinga et al.* remains applicable. Applicants respectfully disagree. As amended the claims clearly exclude the presence of a viral particle containing the DNA molecule. The claims recite that the compound is a plasmid, which excludes adenovirus or any other viral vector.

Since *Guibinga et al.* teach that the activation of the CD28 signal pathway leads to immune responses against the adenoviral vector and since the claims encompass the use of CD28 with an adenoviral vector, there is doubt that the claimed invention would be predictable to those skilled in the art. The claims have been amended to recite that the

compounds are plasmids, which excludes adenoviruses. Accordingly the claimed invention no longer encompasses adenovirus particles. The teachings that prevention of activation of the CD28 pathway inhibits an anti-adenovirus immune response that would otherwise occur if the CD28 pathway was activated no longer raise any doubt as to the predictability of the invention. Furthermore, the claimed invention is not directed at adenovirus vectors and expressly refers to liposomes and cationic amphiphile-nucleic acid complexes. Nothing in *Guibinga et al.* provides any reason to doubt that plasmids or liposomes and cationic amphiphile-nucleic acid complexes which include a CD28 protein or fragment thereof that interacts with CD80/CD86 would not be expected to work. There is nothing in *Guibinga et al.* suggesting that an immune response analogous to the anti-adenovirus response associated with activation of the CD28 pathway reported in *Guibinga et al.* would be induced against a plasmid or a liposome or cationic amphiphile-nucleic acid complex. It is also asserted that the teachings in *Guibinga et al.* indicate that a non-specific immune response induced by activation of the CD28 signaling pathway would also render the expectation of success in practicing the invention unpredictable. *Guibinga et al.* does not discuss inoperability of a plasmid or a liposome or cationic amphiphile-nucleic acid complex due to CD28 signal pathway activation. One skilled in the art reviewing all of the art of record would have no reason to doubt the predictability of success in practicing the claimed invention beyond those embodiments which include adenovirus vectors. The claims have been amended such that adenovirus vectors are not encompassed by the claims. Accordingly, the teachings in *Guibinga et al* do not raise doubt of the predictability of the claimed invention sufficient to support a rejection under the first paragraph of section 112.

The Office has rejected Applicants assertion that *Deonarian* does not support the rejection but rather supports Applicants' assertion. As stated in the previous response, *Deonarian* refers to the inefficiency of receptor mediated, targeted gene delivery and reports that it is inefficient. It has been asserted that the inefficiency reported by *Deonarian* supports the conclusion that the invention is not enabled because the receptor mediated, targeted gene delivery reported by *Deonarian* works at a less than optimal level and receptor mediated, targeted gene delivery of genes encoding therapeutic proteins encompassed by the claims would be unlikely to be effective if the delivery

worked at a less than optimal level. There is nothing in *Deonarian* or any other evidence of record to support the Office's assertion that suboptimal gene delivery indicates a reason to doubt the predictability of the invention. The claimed methods recite "A method of introducing a compound into a cell..." *Deonarian* fails to raise any doubt of the ability of the claimed methods to introduce a compound into a cell. The Office quotes *Deonarian* as stating, "Presently, this approach to gene delivery is much less efficient than viral gene delivery." (Office Action, page 5). Whether or not the present method is less efficient is not relevant to patentability. *Deonarian* ***does not*** state or imply that the current methods are not enabled, rather at most *Deonarian* states that it may be not work as well as viral delivery. However, it is not within the responsibility of the Office to decide to patent only efficient methods. The Office is only to determine whether the claimed method is enabled, which it clearly is. The conclusion provided is unsupported by any reasoning or evidence because *Deonarian* ***never*** states that the method doesn't work. Applicants' assert that the invention is enabled and *Deonarian* supports this assertion.

The Office makes the same mistake when evaluating the *Nakano* reference because the *Nakano* reference supports rather than raises doubts about the enablement. According to the Office,

> *Nakano et al* teach that immune reactivity with plasmid DNA encoding antigenic domains is linked to the injection mode, "Different routes of injection of HCV E2 plasmid can result in quantitatively and qualitatively different humoral immune responses"

(Office Action, page 6). However, the different responses that occur from different routes of administration is not relevant to the enablement of the pending claims. As discussed above, the pending claims recite, in part, "A method of introducing a compound into a cell..." Nothing in the *Nakano* reference raises doubt as to whether or not the claimed method is enabled to introduce a compound into a cell. Rather, as in the case of *Deonarian*, *Nakano* discusses difference that can result from different types of administration. However, this is not relevant to the patentability of the pending claims.

The Office attempts to combine the *Nakano* reference with *McCluskie et al.* and *Torres et al* to support the rejection, but this is not persuasive. The Office continues to

emphasize that different routes of administration "influence the strength and nature of immune responses in mice and non-human primates." (Office Action, page 7). However, the Office has not presented a single argument as to why the claimed method of introducing a compound into a cell is not enabled. Applicants respectfully urge that the reasoning provided to support the rejection is contradicted by the evidence offered to support the reasoning.

Nothing in *Nakano et al.* raises doubts as to whether or not one of ordinary skill in the art would expect the invention to work. Rather, *Nakano et al.* provides those skilled in the art with an expectation that the invention will work.

The evidence of record supports the conclusion that the claims are enabled. The evidence of record supports the conclusion that one having ordinary skill in the art would not doubt Applicants' assertion that the claimed invention is enabled. Weighing the totality of the evidence of record, one skilled in the art would have a reasonable expectation of success. The burden of establishing that the claims are not enabled requires the Office to put forth sufficient reasoning and evidence sufficient to support a conclusion that one skilled in the art would doubt Applicants' assertion that the invention is enabled. Not only has the burden not been met but the evidence of record would lead one of skilled in the art to have a reasonable expectation of success. If the rejection is maintained, Applicants respectfully request that the Office put on the record sufficient reasoning as to why the claimed methods would not be enabled to introduce a compound into a cell.

The claims are enabled. Applicants respectfully request that the rejection under 35 USC 112, first paragraph be withdrawn.

Claim Rejections under 35 USC 103

Claims 1, 3-6, 8, 10, 12, 13, 31, 33, 34, and 37-42 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Sedlacek *et al.* (US 6,358,524) in view of *Wong-Staal et al* (US 2001/0007659) and *Paul et al* (US 5,736,387). Applicants respectfully disagree.

Sedlacek discusses "Target cell-specific non-viral vectors for inserting genes into cells, pharmaceutical compositions comprising such vectors and their use." Although,

Sedlacek discusses a "non viral carrier for the gene to inserted; a ligand which can bind specifically to the desired target cell; a fusion protein for the penetration of the vector into the cytoplasm of the target cell; and the gene to be introduced," (*Sedlacek*, Abstract), the reference fails to discuss or even suggest using the CD28 receptor ligand or fusing the gp41 as part of the ligand.

As noted in the Official Action, the combined teachings of *Wong-Staal et al* and *Paul et al* do not teach delivering a DNA molecule. It is asserted nonetheless that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Wong-Staal et al, Paul et al, and Sedlacek et al* by simply selecting CD28 as the ligand moiety for delivering a DNA molecule to dendritic cells and fusing the ligand with the fusogenic gp41 with a reasonable expectation of success. It is asserted that the ordinary skilled artisan would have been motivated to modify the claimed invention because the gp41 uptake moiety in the chimeric targeting protein provided additional means for gene delivery vector entering into the cells, and it is a matter of optimization and customization for the target cells of interest. Thus, the claimed invention as a whole was clearly *prima facie* obvious in the absence of evidence to the contrary.

The compositions taught in *Sedlacek et al* are distinct and function differently compared to those of *Wong-Staal et al* and *Paul et al* and there would be no motivation to combine them. Neither *Wong-Staal et al* nor *Paul et al*, teaches or suggests using plasmids as a delivery vehicle. Rather, *Wong-Staal et al* and *Paul et al* teach the use of retroviruses that contain RNA, which upon infection is reverse transcribed into DNA that integrates in a host genome. The teachings described in *Wong-Staal et al* and *Paul et al* are directed toward the use and modification of retroviruses and are very different from the use of plasmids, particularly those that include DNA. The ability to incorporate genetic material by integration into the genome of targeted cell is an important reason for using retroviruses as delivery vehicles. One skilled in the art following the teachings of *Wong-Staal et al* and *Paul et al* would not consider producing non-viral particles such as those taught by *Sedlacek et al*, and most definitely would not consider using DNA containing non-viral particles. The modifications of *Wong-Staal et al* or *Paul et al* that the Office suggests would be necessary to produce the claimed invention defeat the

reasons for using retroviral vectors. Such modifications would not be obvious to those skilled in the art. There would be no motivation by those skilled in the art to combine the teachings of *Sedlacek et al* with those of *Wong-Staal et al* or *Paul et al.* Those skilled in the art following the teachings of *Sedlacek et al* would not consider following the teachings of *Wong-Staal et al* or *Paul et al* which are narrowly directed at the use of retroviral vectors to deliver genes to cells.

Furthermore, in establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been led to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from appellants' disclosure, see for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would ***impel*** one skilled in the art to do what the patent applicant has done. (citations omitted; emphasis added)

The Office has identified no "motivating force" that would "impel" persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention. The Office has failed to provide the "motivating force" to combine references that use retroviruses with a reference that uses non-viral particles. As discussed above,

these compositions are drastically different from one another and would not be combined by one of ordinary skill in the art.

Without more specific suggestions in the prior art, there is insufficient motivation to combine the cited references. Furthermore, "focusing on the obviousness of substitutions and differences, instead of the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Son,* 16 U.S.P.Q.2d 1923, 1927 (Fed. Cir. 1990). The Office has focused on the elements of the *Wong-Stall et al* and *Paul et al.* rather than reading the references for what they teach as a whole. When read as a whole it is clear that *Wong-Stall et al* and *Paul et al.* do not discuss or even suggest the use of a plasmid and would not be combined with *Sedlacek et al.*

In addition, it appears that the only motivation that the Office is using to combine the references is the use of the Applicant's specification and hindsight reconstruction, which is strictly forbidden. *In re Fine,* 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."). When assessing whether or not a combination of references would have produced a claimed invention, one must consider the teaching of each reference as a whole without undue emphasis on those features that would support a finding of obviousness. *In re Wesslau,* 147 U.S.P.Q. 391 (C.C.P.A. 1965) (it is impermissible to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the references fairly suggest to one of ordinary skill in the art).

Indeed, it appears that the only guide to picking and choosing particular elements from the prior art appears to have been the present application given that the Office stated, "Given the numerous choice of receptors and fusogens known in the art...." Without Applicants' specification, the Office would not have been able to pick and choose the references since there are "numerous choice of receptors and fusogens known in the art." It is clear that the Office has used the present application as the blueprint for its obviousness rejection. Thus, the combination of references is improper for, at the very least, failure to provide motivation to combine references and for its use of hindsight reconstruction based upon Applicant's disclosure.

The Federal Circuit has recently affirmed the requirement for motivation to combine references, stating that:

> virtually all [inventions] are combinations of old elements. Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed [**10] elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention . . .
>
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and ***with no knowledge of the claimed invention***, would select the elements from the cited prior art references for combination in the manner claimed . . .
>
> To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Yamanouchi Pharm. Co. v. Danbury Pharm, Inc., 231 F.3d 1339 (Fed. Cir. 2000); 56 U.S.P.Q.2D 1641, 1645, citing *In re Rouffet*, 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457-8 (Fed. Cir. 1998) (emphasis supplied).

It appears that the Office has done what Yamanouchi reaffirms should not be done -- used Applicant's specification as a blueprint.

Accordingly, claims 1, 3-6, 8, 10, 12, 13, 31, 33, 34, and 37-42 are not obvious in view of the combination of *Sedlacek et al.* in view of *Wong-Staal et al,* and *Paul et al.* Applicants respectfully request that the rejection of claims 1, 3-6, 8, 10, 12, 13, 31, 33, 34, 37-42 under 35 U.S.C. 103(a) as being unpatentable over *Sedlacek et al.* in view of *Wong-Staal et al,* and *Paul et al.* be withdrawn.

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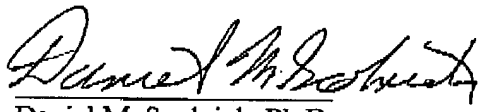
Conclusion

For the foregoing reasons, Applicants respectfully request that 1, 3-6, 8, 10, 12, 13, 33, 34 and 37-42 be allowed. A notice of allowance is earnestly solicited.

Respectfully submitted,



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